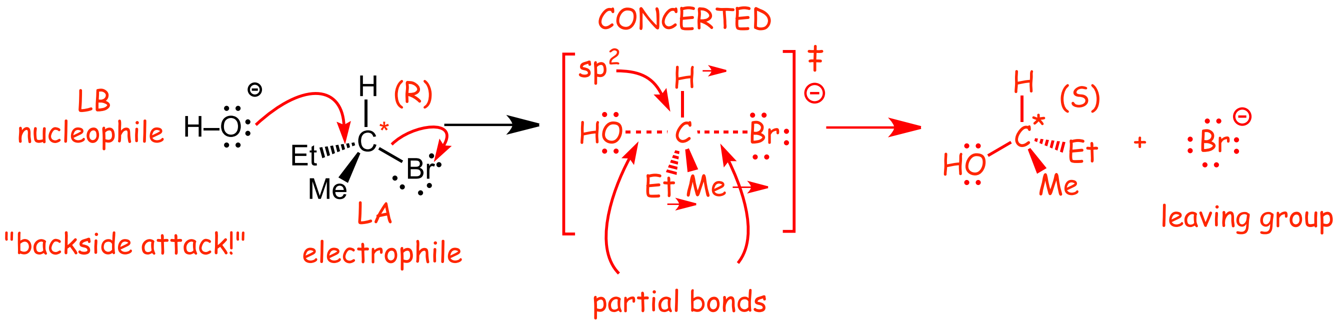
1 Substitutions (Quick Review)

1.1 SN2 Reactions

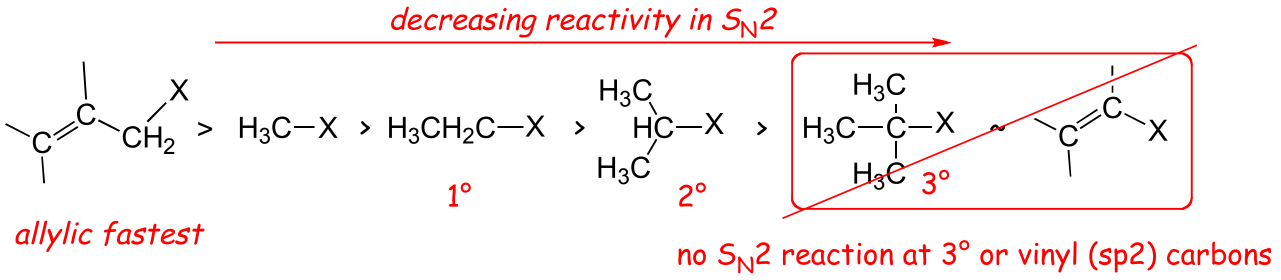


- **CONCERTED reaction**
- This is fundamentally just a Lewis acid/base reaction, the Lewis base has the high energy chemically reactive electrons, which are used to make a new bond to the Lewis acid, and a stronger bond is formed (C-O in the example above) and a weaker bond is broken (C-Br above)
- HO^- is the Lewis Base/**Nucleophile**, the halide is the Lewis acid/**Electrophile,** Br^- is the **Leaving Group**
- A weaker bond is converted into a stronger bond

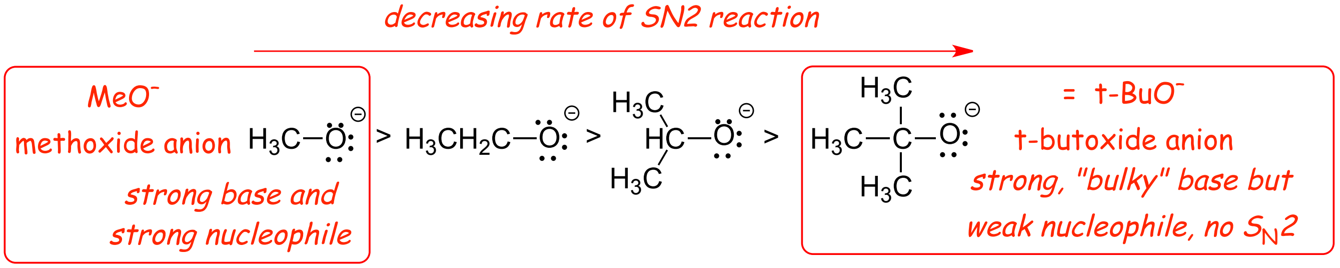
C-Br: B.D.E. ~ 65 kcal/mol (weaker bond)
HO-C: B.D.E. ~ 90 kcal/mol (stronger bond)

Examples of SN2 Reactions: Give the major organic product in the following reactions
- we understand these SN2 reactions a simple Lewis acid/base processes
- identify the Lewis base/NUCLEOPHILE as the reactant with the high energy electrons
- the Lewis acid/nucleophile must react with the Lewis acid/ELECTROPHILE

Reactivity order for SN2, halide structure....



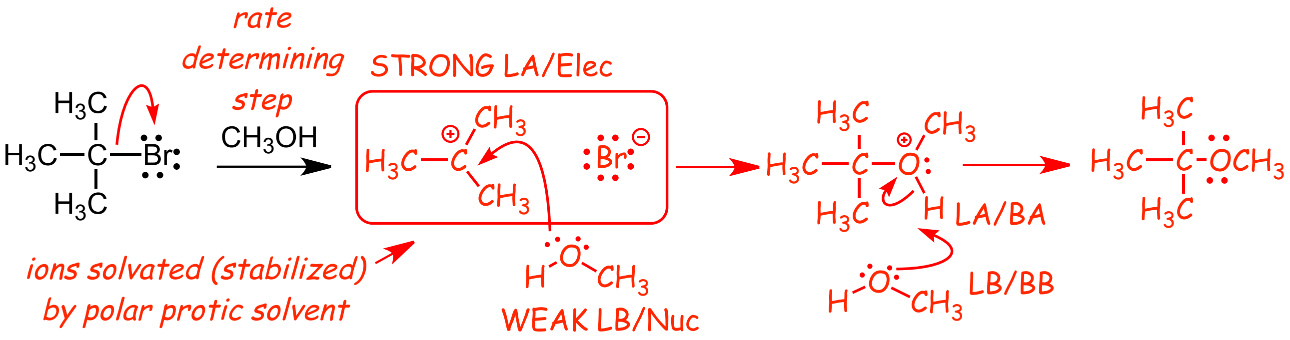
and, nucleophile structure



- SN2 reactions get slower with increasing steric hindrance at the backside of the carbon of the electrophile
- To the extent that there is **no SN2 reaction** at a **tertiary** halide
- SN2 reactions at **methyl** and **allylic** carbons are particularly facile (see below)
- There is **no SN2 at a tertiary or vinyl carbons** because the nucleophile cannot get close enough to form reasonable partial bonds in the transition state due to a steric effect at the other alkyl substituents on the C atoms

1.2 SN1 Reactions

- What happens if we try to do an SN2 reaction with a very weak (e.g. neutral) nucleophile Lewis base?



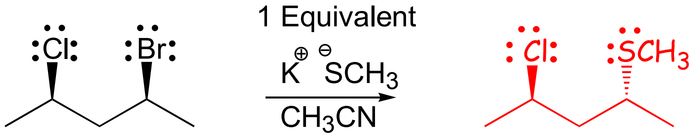
- here we have a nucleophilic substitution reaction BUT......
- we have a 3° halide which is a weak electrophile (backside attack is not possible), can't do S_N2
- H_3COH is a weak nucleophile (no negative charge on the oxygen), shouldn't do S_N2
- H_3COH is also a PROTIC solvent, which should be slow for SN2
- here the solvent "helps" to break the C–Br bond, the reaction is a **solvolysis reaction** (lysis - bond breaking)

1.3 SN1 versus SN2 Reactions

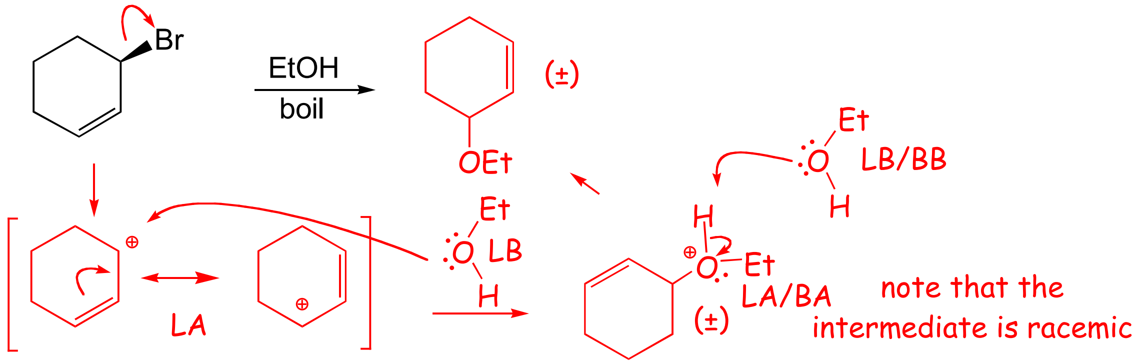
S_N2 favored by:
- 1° > 2° > 3°
- strong nucleophile
- polar *aprotic* solvent

S_N1 favored by:
- 3° > 2° > 1°
- weak nucleophile
- polar *protic* solvent AND heat

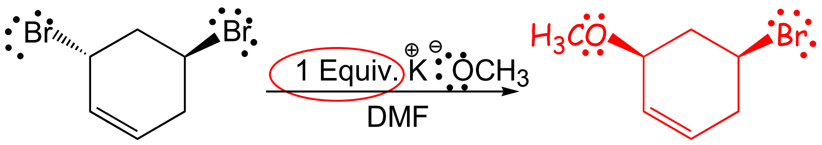
Example Problems: Give the major organic product of reactions



- polar aprotic solvent, strong nucleophile, SN2, Br- better leaving group
- **1 equivalent means exactly the same number of nucleophiles as organic reactants**, which in this context means that there is only enough nucleophile to substitute one of the halide leaving groups



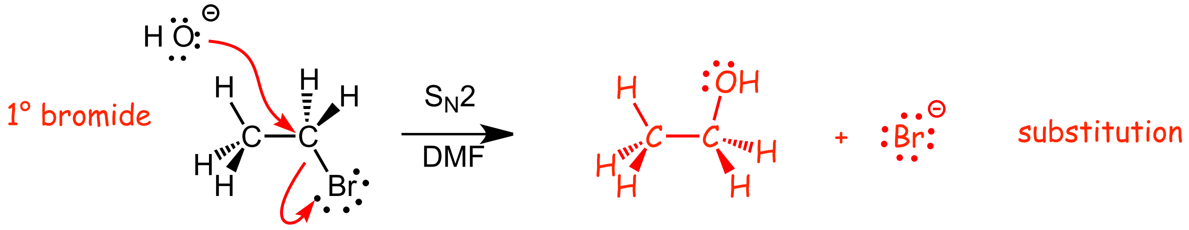
- Polar protic solvent and heat, no strong nucleophile and allylic halide, must be SN1. Need to draw the mechanism to be sure of the product!



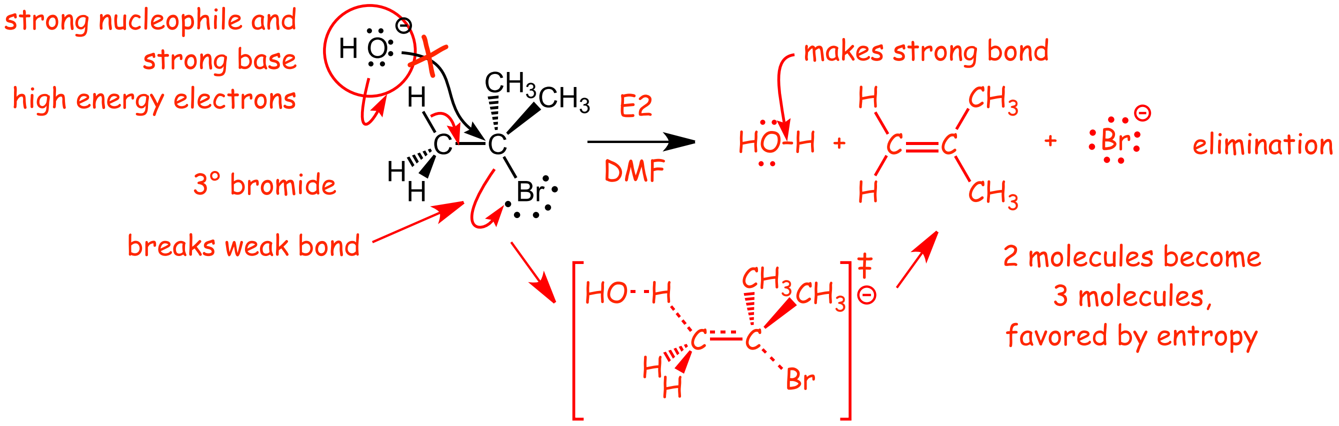
- polar aprotic solvent, strong nucleophile, SN2, allylic position more reactive
- 1 EQUIVALENT will ONLY REACT at the carbon where SN2 will be fastest

4 E2 Elimination Reaction

HERE is straightforward S_N2 at a primary bromide......



- what about this reaction? S_N2 is not possible here (3° bromide), yet there certainly **is a reaction**

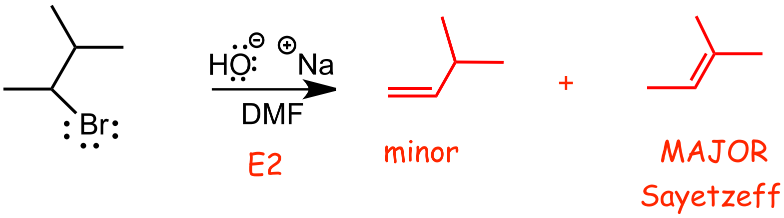


- does E2 instead!
- breaks weak C–Br bond and strong C–H bond, makes strong O-H bond and C=C pi bond
- not as exothermic as S_N2, but the reaction converts 2 molecules into 3, favored by entropy AND "converts" strong -OH base into weak -Br base, this lowers the energy of these electrons, which also helps
- Just like S_N2, all bonds made and broken at same time *(all four!)*
- the $^-$OH acts as a Brønsted base, a **strong base is required for E2!** What we are doing here is using the chemical potential energy (reactive electrons) in the strong base to "drive" this reaction, to make it "go"
- **The reaction is concerted (all four bonds are made and broken at the same time)**

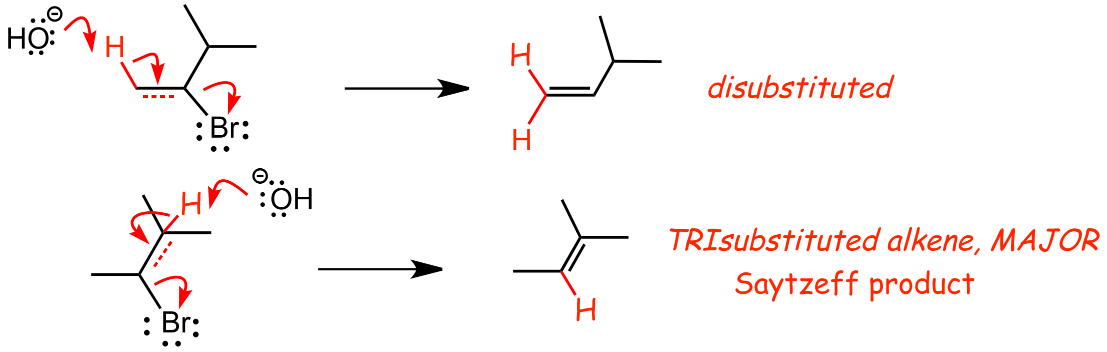
4.1 Product Selectivity in E2: Saytzeff Rule (or Zaitsev, etc.)

The Saytzeff Rule: Most substituted alkene is formed in an E2 reaction, if possible

Example



- When more than one alkene isomer can be formed in an E2 elimination, the more substituted, more stable alkene isomer is usually formed (see an exception below), this more substituted alkene is called the Sayetzeff alkene, after the Russian chemist of the same name
- Sayetzeff's name was translated differently from the Cyrillic into Roman alphabet in different countries, hence **Sayetzeff can be spelled multiple ways, Zaitsev is another common spelling**
- consider how these two E2 products are formed



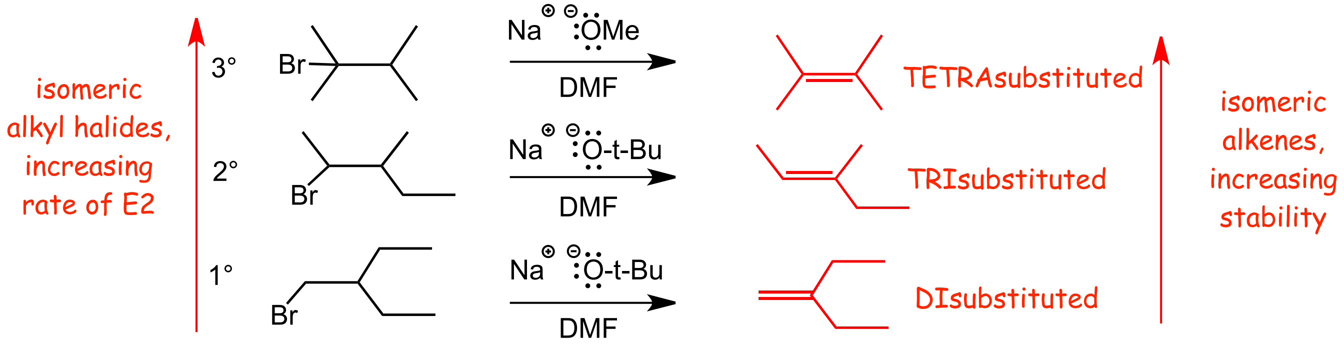
Recall, the most substituted alkene is always the most stable alkene isomer

- the Sayetzeff/Zaitsev alkene is the most substituted of all possible structurally isomeric alkenes that can be formed in an elimination reaction
- E2 eliminations will always form the Sayetzeff/Zaitsev alkene unless there are steric inhibitions, see below

4.2 Reactivity Order for E2

•Decreasing reactivity order: 3° > 2° > 1° halide

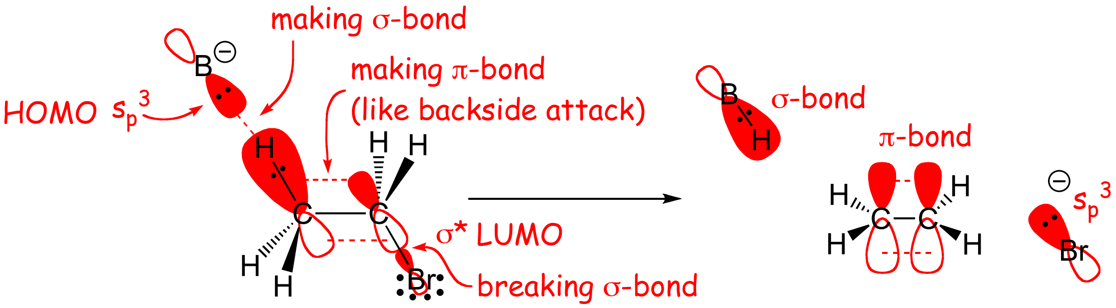
Example



- Elimination from a 3° halide tends to give a more substituted alkene product, tends to be faster
- This is one way that we can easily distinguish the possibilities of SN2 versus E2, there is simply no SN2 at a tertiary halide, but E2 eliminations tend to be facile (assuming a strong enough base)

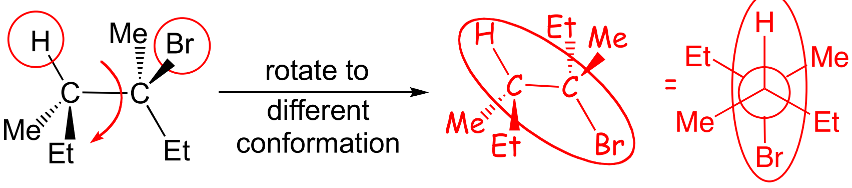
4.3 Stereochemistry of E2 Reaction

- Again, Molecular Orbital theory provide a very informative picture
- We need to make and break ALL FOUR bonds at the same time, the reaction is concerted
- We need to make the new bonds by **overlapping the HOMO and the LUMO IN PHASE to make new bonding molecular orbital**



- The 2 sigma M.O.s on the central carbons (associated with the breaking C-H and C-Br bonds) become the pi M.O.s (bonding and antibonding)
- The 2 sigma M.O.s therefore must be parallel in order to be able to make the new pi-bond
- The H and leaving group (Br) must be coplanar (periplanar), and preferably "anti"
- The electrons in the breaking C-H sigma bond are used to make the new pi-bond, overlap occurs with the anti-bonding M.O. associated with the breaking C-Br bond best as shown, i.e. analogous to "backside attack" in the SN2 reaction, this is the origin of the requirement for ANTI- in addition to co-planar
- **Only One conformation will tend to be reactive in an E2 Reaction**

C-H and C-Br bonds NOT anti-coplanar

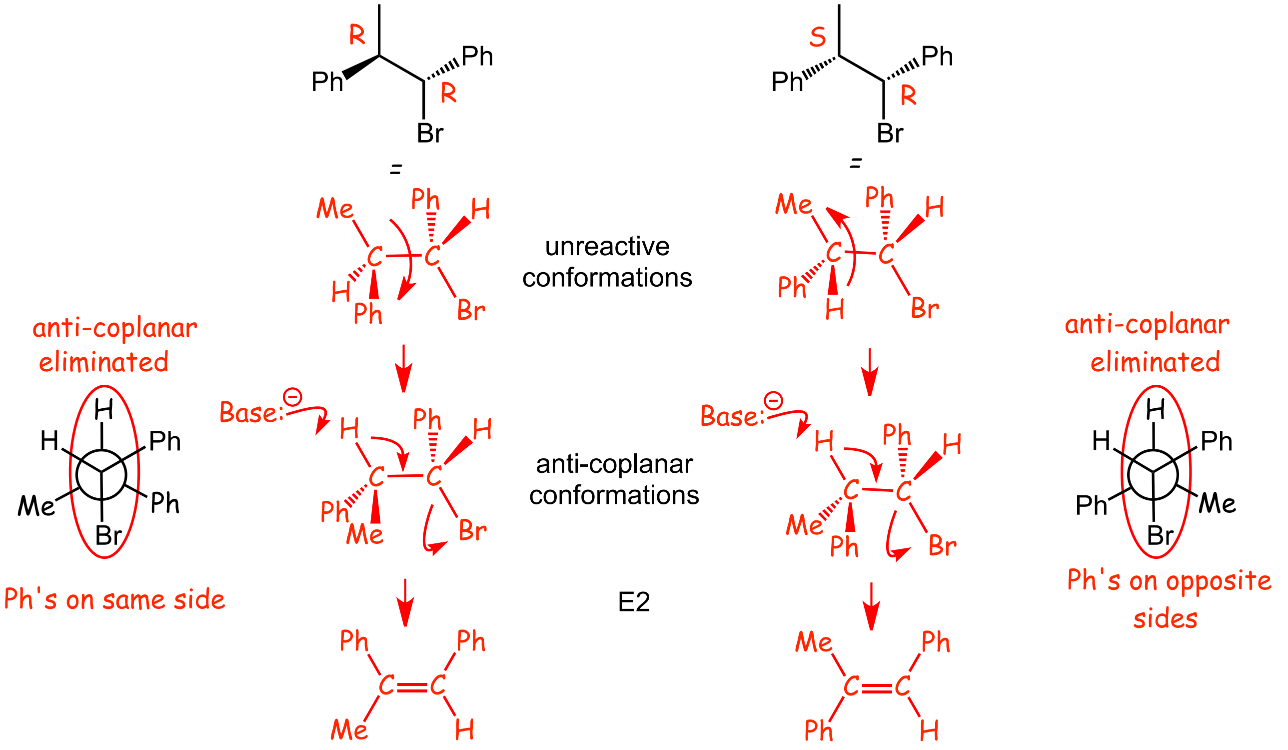


anti-coplanar is the "reactive conformation"

- The reactive conformation must be attained BEFORE reaction can occur

Example: give the major products of the E2 reactions of:

(1R)-bromo-(1,2R)-diphenylpropane AND (1R)-bromo-(1,2S)-diphenylpropane

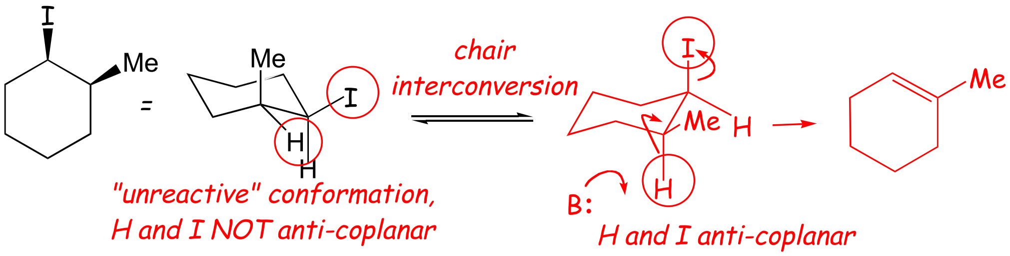


cis-diphenyl alkene formed

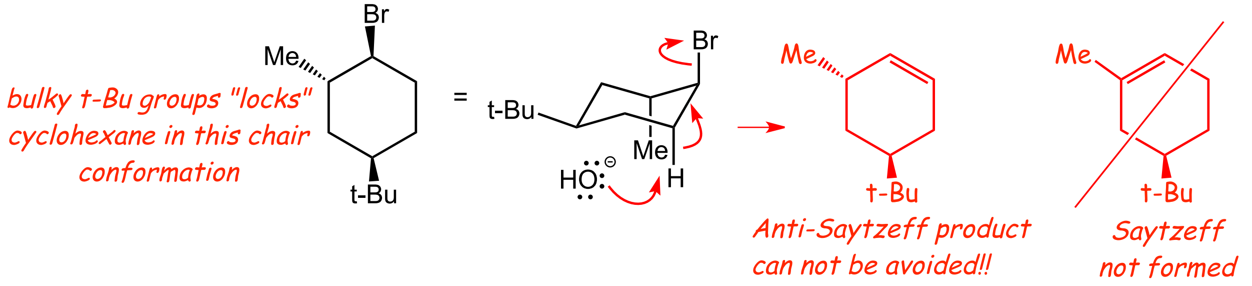
trans-diphenyl alkene formed

- **The reaction is stereospecific, different isomeric halides give different isomeric alkenes because the reaction is concerted**

Example: give the major product of the E2 reaction of (1R)-iodo-(2S)-methylcyclohexane

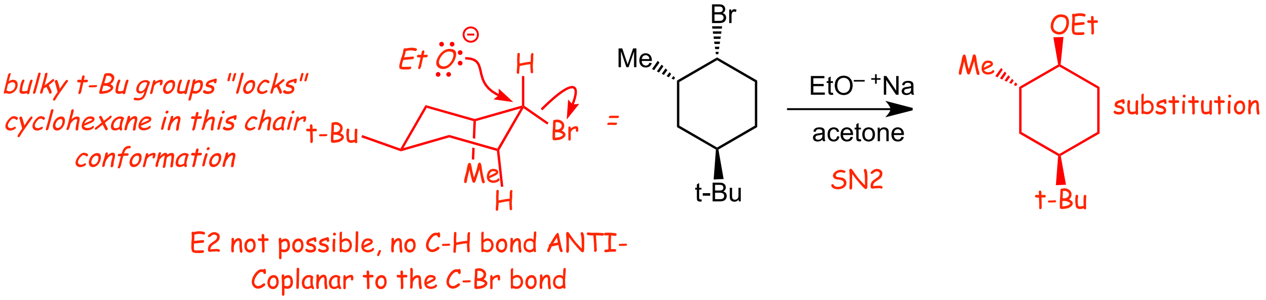


Example: give the major product of the E2 reaction of the following compound



- The cyclohexane is "locked" into the chair that has the LARGE t-butyl substituent in the equatorial position, i.e., the energy difference between the two chairs is so large that the one with the axial t-butyl is present at such low concentration that it can be ignored
- In this conformation, the C-H bond that is anti-coplanar to the C-Br bond MUST give the Anti-Sayetzeff alkene

Example: give the major product of the following reaction......

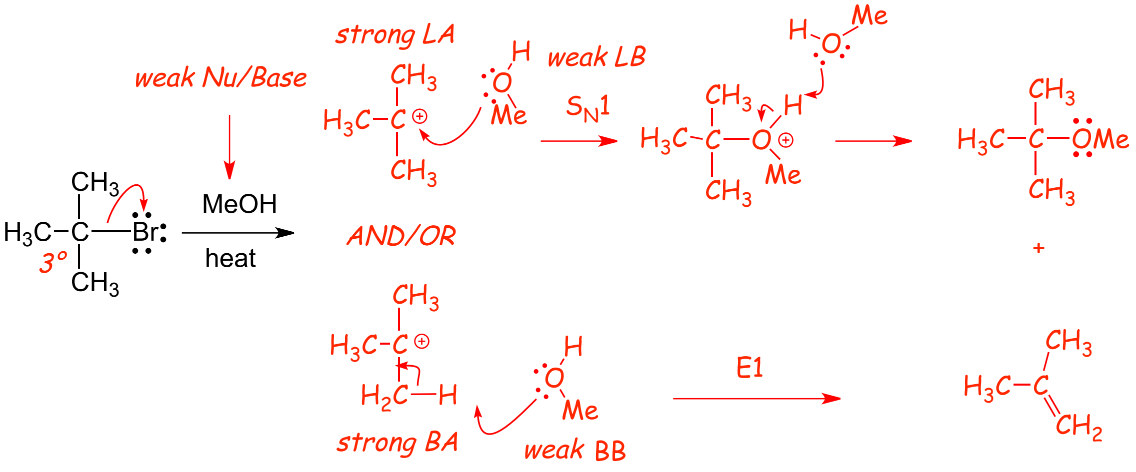


- Again, the Br is "locked" into an equitorial position because of the LARGE t-butyl group
- In this conformation (chair) that are NO anti-coplanar C-H bonds, therefore E2 is NOT POSSIBLE and SN2 is the only reasonable reaction

5 E1 Elimination Reaction

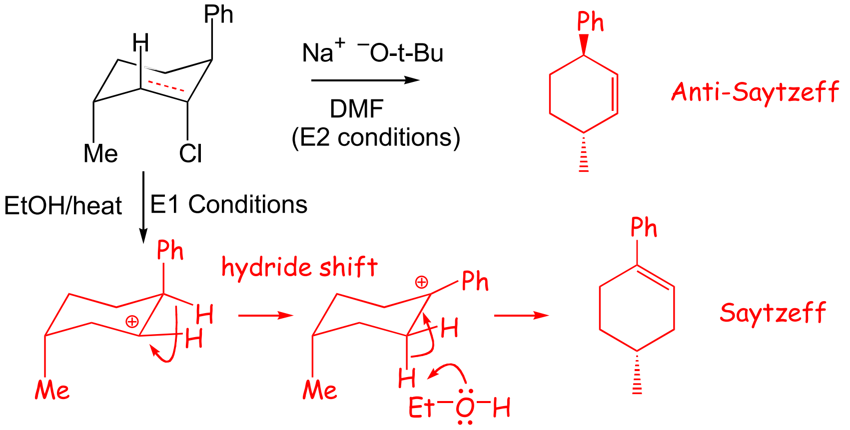
- elimination initiated by 1st-order heterolysis

Example: a 3° halide with a poor nucleophile, poor Brønsted base and in a polar protic solvent



- the intermediate cation is a strong electrophile that can react with the weak nucleophile MeOH via SN1
- the intermediate cation is ALSO a VERY STRONG Brønsted acid, stronger than hydrochloric acid (pKa < -10)
- The intermediate cation can, therefore, react with the weak Bronsted base MeOH in a Bronsted acid/base reaction to give an alkene ELIMINATION product
- E1 elimination because **one molecule** is involved in **the rate determining step** (kinetically first order)
- SN1 and E1 are often competitive, they have the SAME rate determining step, the reactions "partition" at the cation intermediate
- It is difficult to select conditions that favor E1 (high temperature can help due to the temperature dependence of entropy), i.e. not useful "synthesis" reaction - see later

Example: Give the expected ELIMINATION products (ignore substitution) under the following conditions

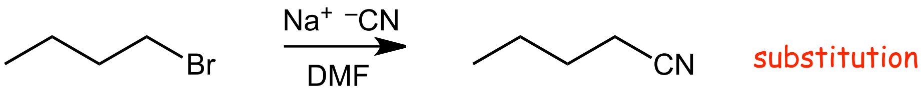


6 Distinguishing E1, E2, SN1 and SN2 Reactions

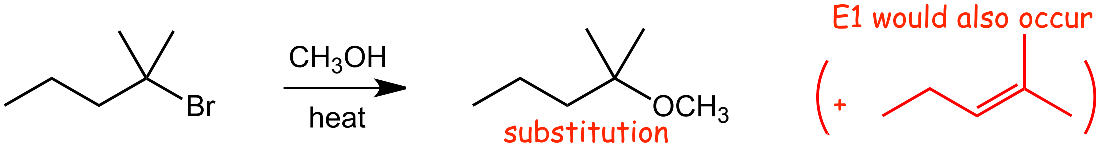
- Reality - the mechanisms are often mixed : However, favored conditions are........

S_N2 - 1° halide, aprotic solvent, strong nucleophile, weak base
S_N1 - 3° halide, protic solvent, weak nucleophile, weak base
E2 - 3° halide, aprotic solvent, weak nucleophile, strong base
E1 - 3° halide, protic solvent, but in reality they are difficult to favor!

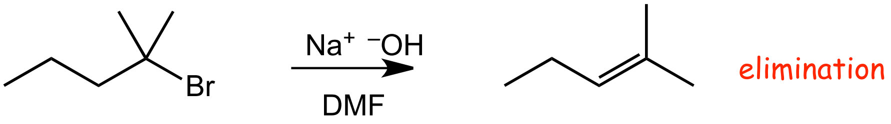
Examples:_What was the mechanism that resulted in the PROVIDED organic product? (there may be other reaction products, but the questions ask about the provided ones only)



strong Nu and base, polar aprotic, but 1°, therefore must be S_N2

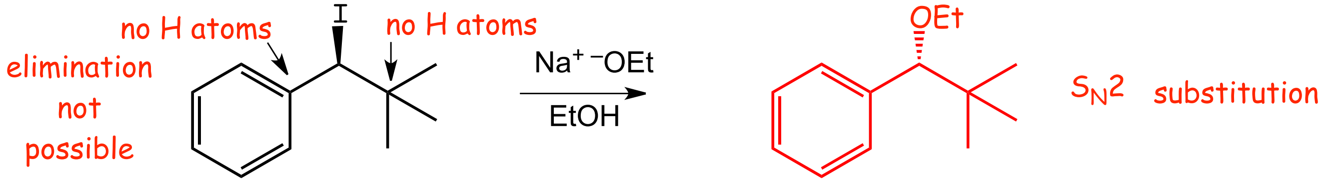


3° halide, weak Nu and weak base, polar protic and heat, must be S_N1



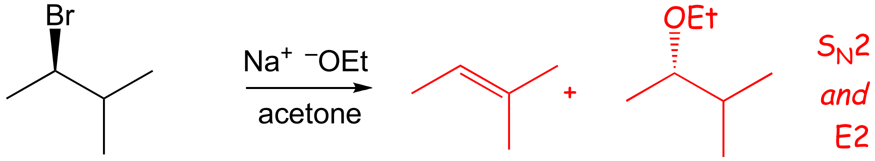
3° halide, strong Nu and base, polar aprotic, must be E2

Example: give the major products of the following reactions and identify the reaction mechanisms



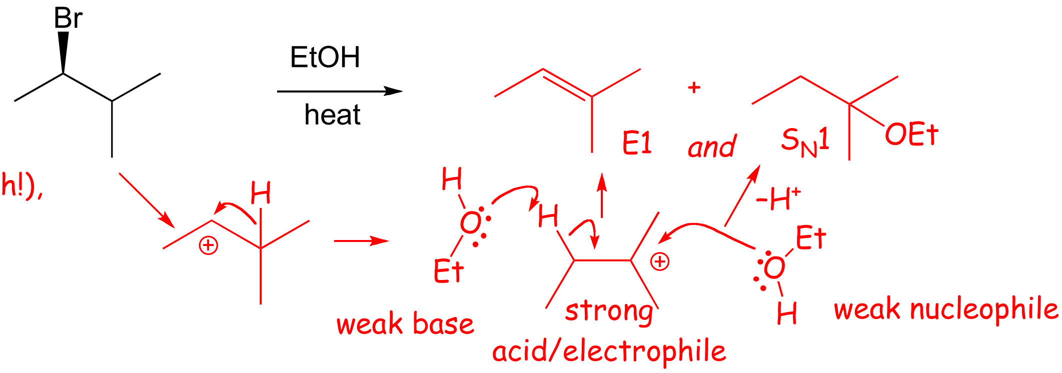
"allylic", strong base/Nu, polar protic, E2 not possible, must be S_N2

- There is no REQUIREMENT for an SN2 reaction to be in a polar aprotic solvent, they are faster in aprotic solvents but in reality many are actually performed in protic solvents for convenience



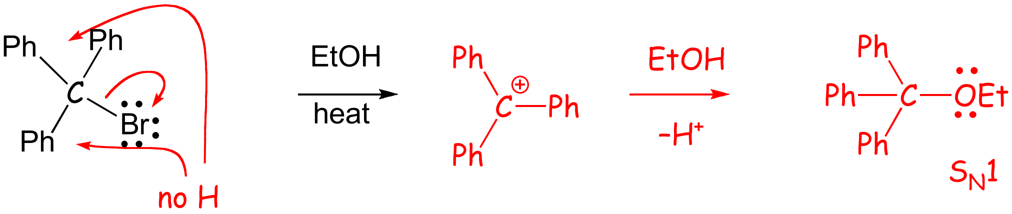
2° halide (tough!), strong base and strong Nu, polar aprotic - mixture!

- Secondary halides don't favor any mechanism in particular and often undergo more than one reaction



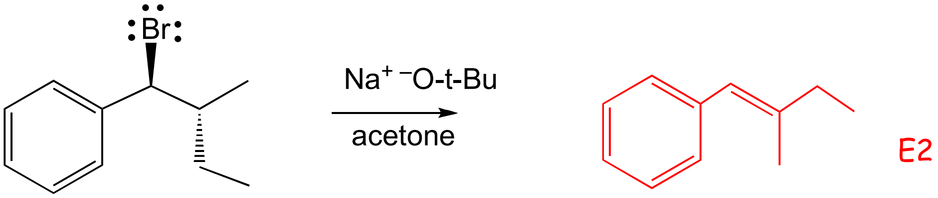
2° halide (tough!),
weak base/Nu,
polar aprotic -
mixture!

- It is usually a good idea to draw out at least a partial mechanism when carbocation intermediates are involved to avoid missing any rearrangements
- SN1 and E1 are often competitive, unless elimination is not possible because there are no adjacent hydrogen atoms



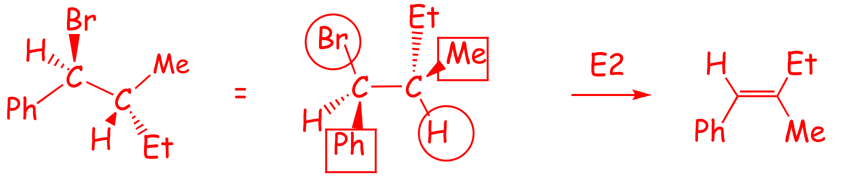
3° halide, weak base/Nu, polar protic - No elimination possible - S_N1

- Elimination is not possible in this case



3° halide strong base but weak nucleophile so can't do S_N2, polar aprotic, must be E2

get the
stereochemistry
of the alkene
product correct!



redraw as 3D structure

Br- and -H anti-coplanar
Ph and Me on the "same side"

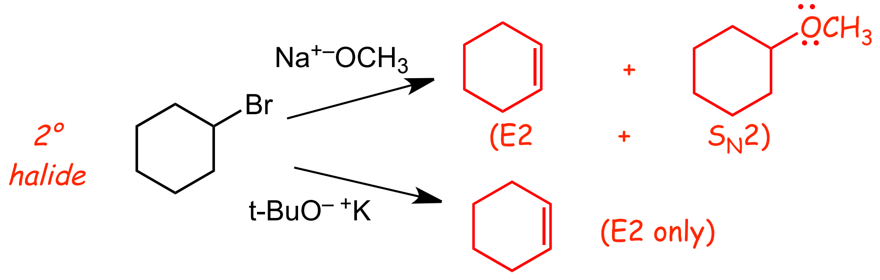
same as above

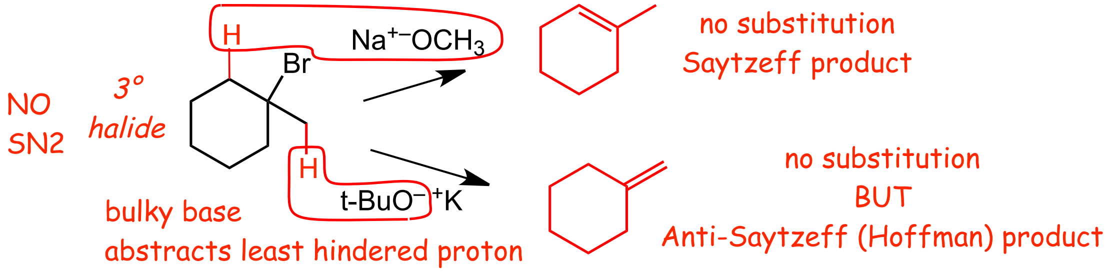
- Note the use of the t-butoxide anion **bulky base** to force E2 elimination
- For E2 eliminations where there is stereochemistry in the reactant, you will usually have to setup the correct conformation for elimination (anti-coplanar) in order to get the correct stereochemistry in the alkene product

7 Elimination Using Bulky (Sterically Hindered) Bases

- The products of E2 eliminations can be different for 2 versus 3° halides with or without bulky bases

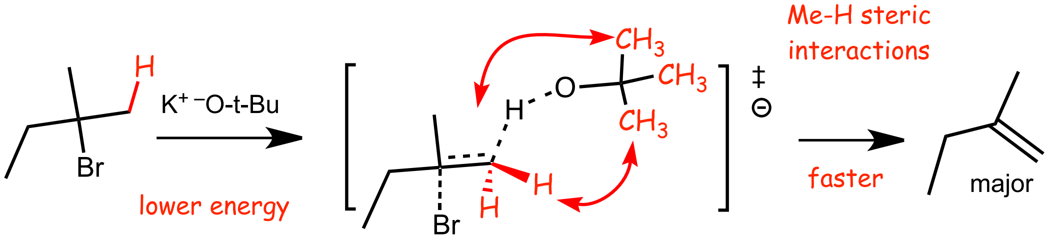
Examples:





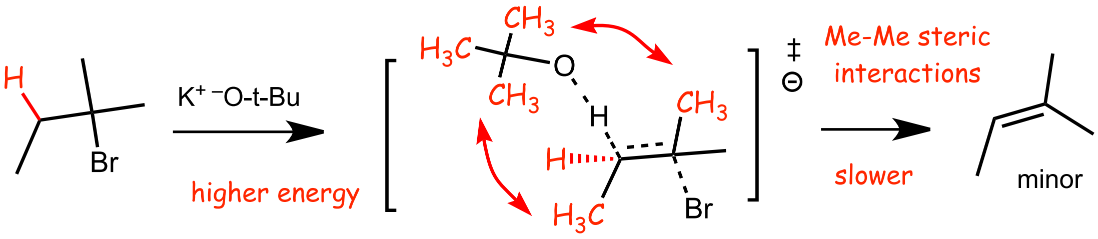
Looking at the **Transition States** can explain these product distributions

- the **fstest** reaction occurs, the reaction is **kinetically controlled**



transition state for MAJOR product

- The transition state for formation of the MAJOR product has CH3-H electron repulsion/steric effects, which costs LESS energy that CH3-CH3 electron repulsions/steric effects below, the transition state is thus lower in energy, the reaction is faster and this reaction forms the MAJOR product



transition state for MINOR product

- The transition state for formation of the minor product has CH3-Ch3 electron repulsion/steric effects, which costs MORE energy that CH3-H electron repulsions/steric effects in the reaction that forms the major product, the transition state is thus higher in energy, the reaction is slower and this reaction forms the minor (Hoffman) product

In Summary

- A **non-bulky** with a **3° halide** forms the **most substituted alkene** (normal Saytzeff product)
- **But**, a **bulky base** with a **3° halide** forms the **least substituted alkene (Hofmann product)** for steric reasons

10 Reaction Summary

Do NOT start studying by trying to memorize these reactions!
Work as many problems as you can with this list of reactions in front of you, if necessary, so that you can get through as many problems as you can without getting stuck on the reagents/conditions. AFTER you have worked all of the problems, just before an exam, then do the following:

- Cover the entire page of reagents/conditions with a long vertical strip of paper, see if you can write down the reagents/conditions for each reaction, check to see which you get correct, if COMPLETELY correct, circle Y, if incorrect or even slightly incorrect, circle N. In this way you keep track of what you know and what you don't know.
- Keep coming back to this list and so the same thing only for those reactions you circled N, until all are circled Y.
- Knowing the reagents/conditions on this page is INSUFFICIENT to do well on an exam since you will ALSO need to recognize how to use and solve reaction problems in different contexts, this page ONLY helps you to learn the reagents/conditions that you have **not YET** learned by working problems.

ALSO, SN2 reactions in particular can occur in MANY DIFFERENT CONTEXTS, knowing the reactions summarized here is INSUFFICIENT for you to solve substitution and elimination reaction problems